PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 162784.3 DAB	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/IL2005/001166	International filing date *(day/month/year)* 08 November 2005 (08.11.2005)	Priority date *(day/month/year)* 08 November 2004 (08.11.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CAN-FITE BIOPHARMA LTD.		

This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 08 May 2007 (08.05.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/001166	08.11.2005	08.11.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/00 A61K31/7076 A61P19/08 A61P19/10

Applicant
CAN-FITE BIOPHARMA LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Paul Soto, R Telephone No. +49 89 2399-7346

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/001166

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	1-26 (see separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

1. Reference is made to the following documents:

   D1: WO 2005/084653 A (CAMBRIDGE BIOTECHNOLOGY LIMITED; PRITCHARD, MARTYN; OUZMAN, JACQUELINE) 15 September 2005
   D2: WO 2004/045627 A (CAN-FITE BIOPHARMA LTD; FISHMAN, PNINA) 3 June 2004
   D3: WO 2004/078184 A (CAMBRIDGE BIOTECHNOLOGY LTD; RICHARDSON, PETER) 16 September 2004
   D4: WO 01/19360 A (CAN-FITE TECHNOLOGIES LTD; FISHMAN, PNINA; CAN-FITE BIOPHARMA LTD) 22 March 2001, cited in the application
   D5: WO 00/72799 A (THE UNIVERSITY OF VIRGINIA PATENT FOUNDATION; LINDEN, JOEL, M; SULLIVA) 7 December 2000

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

2. The present application according to **claim 1** relates to a method for the treatment of accelerated bone resorption in a mammal subject comprising administering an effective amount of an A3 adenosine receptor agonist (A3AR agonist). **Claim 11** is directed to a pharmaceutical composition for the treatment of accelerated bone resorption the composition comprising an amount of an A3AR agonist, the amount being effective to inhibit bone resorption in a mammal subject. Finally, **claim 19** is directed to the use of an A3AR agonist for the preparation of a pharmaceutical composition for the treatment of accelerated bone resorption.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

3. Claims 1-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article

34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

D2 discloses the treatment of inflammatory arthritis by oral administration of adenosine A3 receptor agonists, preferably with the compounds IB-MECA and Cl-IB-MECA. The loss of bone was also measured (see histology score in example 3C) and it is reported that bone loss was markedly lower in the subjects treated with IB-MECA. **D2** is therefore regarded as novelty destroying for present **claims 1-26**.

D3 discloses compounds of general formula (I) and (II) that are selective agonists of A2A and/or A3 receptors and are useful for the treatment of inflammatory or auto-immune diseases, including rheumatoid arthritis, osteoporosis and bone resorption diseases. The formula (I) and (II) in **D3** do however not cover the compounds of formula (I) of present claims 7, 15 and 23 because they present a NH_2 at the 6 position. **D3** is regarded as novelty destroying for present **claims 1-6, 11-14 and 19-22**.

D4 discloses the same adenosine A3 receptor agonists as in the present application in connection with the treatment of leukopenia and inhibition of abnormal cell growth and proliferation. This is novelty destroying for present **claims 11-18**. Is it noted that the technical feature "for the treatment of accelerated bone resorption" in present independent claim 11 does not limit in any way the scope of said claim. A pharmaceutical composition is characterised by the ingredients present therein and not by the therapeutic application intended for it. Thus, not only **D4** but also any prior art document disclosing A3AR agonists as therapeutic agents is novelty destroying for the pharmaceutical compositions claimed in the present application.

5. As far as the subject-matter of the claims is not novel, no inventive step can be recognised. Thus, the present application does also not meet the requirements of Art. 33(3) PCT.

6.1. Claims 11-18 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2. For the assessment of the present claims 1-10 and 19-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (present claims 1-9), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (present claims 19-26).

Re Item VI
Certain documents cited

7. Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2005/084653	15/09/2005	04/03/2005	16/09/2004